## REMARKS

Claims 1-26 and 30-31 are currently pending in the application. By this amendment, claims 1, 6, 14 17, 21, 25 and 30-31 have been amended. The foregoing separate sheets marked as "Listing of Claims" show all the claims in the application, with an indication of the current status of each.

**Drawings**

Replacement drawings filed on 02/02/2004 have been objected to because, according to the Examiner, they did not properly indicate that they were "replacement" or "new" sheets. Applicant has herewith filed copies of the formal drawings for this application in which each drawing is properly labeled "Replacement Sheet" in the top margin. The submission includes copies of the original, prior version of the drawings.

In view of the foregoing, Applicant respectfully requests withdrawal of this objection.

**Claim Rejections: 35 USC § 112**

Claim 25 stands rejected under 35 USC §112, second paragraph, ostensibly due to being indefinite due to the recitation of the phrase "algebraic manipulations relating full and reduced ray mixture models".

Claim 25 has hereby been amended to recite that the full ray and reduced ray mixture models are "compared". Support for this amendment is found, for example, in the specification on page 12 at line 20, which states in the legend for Figure 28, which states that the data represents the estimated dose-response curve on the full ray projected onto the reduced ray under the hypothesis of no effect of malathion compared to the observed dose-response curve on the reduced ray using the SAR interaction threshold model. Applicant submits that this amendment thus does not add any new matter, and respectfully requests entry of the amendment.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

**Claim Rejections: 35 USC § 102(b)**

Claim 14 stands rejected under 35 USC § 102(b) as anticipated by Gennings et al., (hereinafter "Gennings 1997", *Journal of Agriculture, Biological and Environmental Statistics*, 1997, vol. 2, pages 198-211). This rejection is traversed.

One novel feature of the present invention is the use of interaction threshold modeling to analyze data. This type of modeling was developed by the inventors after the Gennings 1997 reference, and the Gennings 1997 reference does not describe, show or use an interaction threshold model for data analysis. Rather, Gennings 1997 describes and utilizes a dose threshold additivity model, which is mathematically distinct from an interaction threshold model, and which cannot provide the type of inference that is provided when an interaction threshold model is employed. The following section provides the Examiner with a detailed mathematical analysis and comparison of the two different models.

***Distinguishing between a dose threshold model and an interaction threshold model:***

The *threshold additivity model* is defined in Gennings 1997 equation (1.1) on page 201 as

$$\mu_{ij}^{\lambda} = \begin{cases} \beta_0, & \text{if} \sum_{i=1}^{c} \beta_i x_{ij} < \delta \\ \beta_0 + \sum_{i=1}^{c} \beta_i x_{ij} - \delta, & \text{if} \sum_{i=1}^{c} \beta_i x_{ij} \geq \delta \end{cases}$$

As stated in the paragraph located directly after equation 1.1 on page 201, "This [threshold additivity] model assumes that concentrations "below" the hyperplane, defined as $\sum_{i=1}^{c} \beta_i x_{ij} = \delta$, yield an effect equivalent to background $\beta_0^{1/\lambda}$; and concentrations "above" the threshold plane result in a concentration-effect trend." Further, as can be seen by the term $\text{if} \sum_{i=1}^{c} \beta_i x_{ij} \geq \delta$, the form of the model "above" the dose threshold is also an additivity model characterized by the sum of the linear terms, $g(\mu_{add}) = \beta_0 + \sum_{i=1}^{c} \beta_i x_i - \delta$. This passage further states that the so-called *link function* relating the mean $\mu$ and the threshold model is the power function, $\mu^{\lambda}$. Applicant notes that a general form for a link function is g($\mu$). Generalized linear models and link functions were

known in the art at the time; for example, as stated in the present application, McCullagh and Nelder (1989) provide a general discussion of generalized linear models and link functions.

It is important to note that the statement of the threshold additivity model in Gennings 1997 requires the background response region to be constant, as defined by the single parameter $\beta_0$, for doses such that $\sum_{i=1}^{c} \beta_i x_{ij} < \delta$ . This region is depicted in Figure 1, as the flat section (with zero slope) near the origin of the graph. As defined in the 1st paragraph of Gennings 1997, a *threshold* is defined as "exposure levels below which the background response results, while levels exceeding the threshold result in a "dose-response" trend."

The Gennings 1997 definition of a threshold (which is more recently referred to in the art as a 'dose threshold') and the corresponding threshold additivity model described in Gennings 1997 are in sharp contrast to the *interaction threshold* defined in the present application. Paragraph [0853], on page 68 of the application states that the "generalized linear interaction threshold model describing the relationship between the response and the doses of the $c$ chemicals in combination" is given by

$$g(\mu) = \begin{Bmatrix} \beta_0 + \sum_{r=1}^{c} \beta_r x_r, & x_c \le Q(x_1, x_2, ..., x_{c-1}) \\ \beta_0 + \sum_{r=1}^{c} \beta_r x_r + \sum_{r=1}^{c-1} \sum_{s=r+1}^{c} \beta_{rs} x_r x_s + & \\ \sum_{r=1}^{c-2} \sum_{s=r+1}^{c-1} \sum_{u=s+1}^{c} \beta_{rsu} x_r x_s x_u + & x_c > Q(x_1, x_2, ..., x_{c-1}) \\ ... + \beta_{12...c} x_1 x_2 ... x_c & \end{Bmatrix}$$

In this equation, which is reproduced in Appendix A for clarity, it is assumed that the interaction threshold boundary "that separates the dose space into regions of interaction and additivity" (paragraph [0848]) … "can be defined such that the value of the $c^{th}$ component can be expressed as a function of the remaining $c$-1 chemicals, i.e.,

$$x_c = Q(x_1, x_2, ..., x_{c-1}).$$"

For the interaction threshold model, the region where $x_c \le Q(x_1, x_2, ..., x_{c-1})$ is associated with an additivity model $g(\mu) = \beta_0 + \sum_{r=1}^{c} \beta_r x_r$; however, the region where $x_c > Q(x_1, x_2, ..., x_{c-1})$ is associated with a more general response surface model that accommodates higher order terms for interaction. Continuing to paragraph [0854], "the model can be made continuous by requiring the values of g($\mu$) at the threshold boundary to be equal." Applicant notes that, as would be understood by those of skill in the art, the above equation is a generalized linear model. As stated in the application in paragraph [0098],

$$\left\{ \begin{array}{ll} \beta_0 + \sum_{r=1}^{c} \beta_r x_r, & x_c \le Q(x_1, x_2, ..., x_{c-1}) \\ \beta_0 + \sum_{r=1}^{c} \beta_r x_r + \sum_{r=1}^{c-1} \sum_{s=r+1}^{c} \beta_{rs} x_r x_s + & \\ \sum_{r=1}^{c-2} \sum_{s=r+1}^{c-1} \sum_{u=s+1}^{c} \beta_{rsu} x_r x_s x_u + & x_c > Q(x_1, x_2, ..., x_{c-1}) \\ ... + \beta_{12...c} x_1 x_2 ... x_c & \end{array} \right\}$$

may be embedded in a general nonlinear model when a general nonlinear model should be used, i.e. in cases where a generalized linear model is not appropriate. This is also reflected in amended claim 14.

The interaction threshold model of the present invention is thus distinct from the threshold additivity model of Gennings 1997 in that, in the interaction threshold model, neither piece of the model (i.e. neither #1 or #2 of the formula shown in Appendix A) is considered to be equivalent to a constant background response region. (Recall that, as stated above Gennings 1997 requires the background response region to be constant, as defined by the single parameter $\beta_0$, for doses such that $\sum_{i=1}^{c} \beta_i x_{ij} < \delta$). Instead, in the interaction threshold model, the term associated with the fewer parameters, $g(\mu) = \beta_0 + \sum_{r=1}^{c} \beta_r x_r$ (which is defined in paragraph [0838]), is a model for additivity. Of the two models, only the interaction threshold model allows for interaction between chemicals which is parameterized with higher degree terms and is allowed only in the region where $x_c > Q(x_1, x_2, ..., x_{c-1})$. Claim 14 has hereby been amended to include the description of the interaction threshold model as per paragraphs [0853] and [0098] of the present

application, thereby clearly rendering the subject matter of claim 14 distinct from that of Gennings 1997.

In summary, Gennings 1997 does not anticipate the present invention as recited in claim 14. Gennings describes a *threshold additivity model* which is distinct from the *interaction threshold model* of the present invention, and which cannot be used to perform the same types of analyses or to draw the same types of conclusions about data as can the interaction threshold model of the present invention.

In view of the foregoing, Applicant respectfully requests reconsideration of claim 14 and withdrawal of this rejection.

**Claim Rejections: 35 USC § 103(a)**

Claims 1-13 and 15-26 stand rejected under 35 USC § 103(a) as unpatentable over Gennings et al. (hereinafter "Gennings 1998", *Journal of Agriculture, Biological and Environmental Statistics*, 1998, vol. 3, pages 1-16), in view of Gennings (1997) as above. This rejection is traversed.

With respect to the rejection of claims 15-26, which depend from claim 14, the inapplicability of Gennings 1997 to the subject matter of claim 14 has been discussed in detail above. Briefly, neither piece of the present interaction threshold model is considered to be equivalent to a constant background response region, whereas Gennings 1997 requires the background response region to be constant. Further, only the interaction threshold model allows for interaction between chemicals which is parameterized with higher degree terms and is allowed only in the region where $x_c > Q(x_1, x_2, ..., x_{c-1})$.

Applicant submits that the deficiencies of Gennings 1997 are not cured by Gennings 1998. Pages 4-5 of Gennings 1998 state that "the threshold additivity model for the combination of $c$ chemicals at $\mathbf{d} = [d_1, d_2, ..., d_c]'$ is

$$\mu_{\mathbf{d}} = \begin{Bmatrix} 1/(1+\exp(-\beta_0)), & \sum_{i=1}^{c} \beta_i d_i < \delta^* \\ 1/(1+\exp(-(\beta_0 + \sum_{i=1}^{c} \beta_i d_i - \delta^*))), & \sum_{i=1}^{c} \beta_i d_i \geq \delta^* \end{Bmatrix},"$$

Since this is for an analysis of proportional data, a logit link is used, i.e., $g(\mu) = \log\left(\frac{\mu}{1-\mu}\right)$. So the model can be equivalently written as

$$g(\mu_d) = \log\left(\frac{\mu_d}{1-\mu_d}\right) = \begin{Bmatrix} \beta_0, & \sum_{i=1}^{c} \beta_i d_i < \delta^* \\ \beta_0 + \sum_{i=1}^{c} \beta_i d_i - \delta^*, & \sum_{i=1}^{c} \beta_i d_i \geq \delta^* \end{Bmatrix}.$$

It is important to note that, as is the case for the model described in Gennings 1997, the statement of the threshold additivity model in Gennings 1998 requires the background response to be constant, here defined by the single parameter $\beta_0$, for doses such that $\sum_{i=1}^{c} \beta_i d_i < \delta^*$.

Also as is the case for Gennings 1997, this Gennings 1998 model is distinct from the *interaction threshold* defined in the patent application (and now recited in claim 14) in that neither piece of the latter is equivalent to a constant background response. Instead, the piece associated with the fewer parameters is a model for additivity: $g(\mu) = \beta_0 + \sum_{r=1}^{c} \beta_r x_r$ (which is defined in paragraph [0838]). In the threshold additivity model, the form of the model "above" the dose threshold is also an additivity model, $g(\mu_{add}) = \beta_0 + \sum_{i=1}^{c} \beta_i x_i - \delta$, characterized by the sum of the linear terms. Of the two models, only the interaction threshold model allows for interaction between chemicals which is parameterized with higher degree terms and is allowed only in the region where $x_c > Q(x_1, x_2, ..., x_{c-1})$. In other words, the interaction threshold model (for both a response surface and along a fixed-ratio ray) the piece associated with the additivity region includes linear terms for each chemical in an additivity model. This is not the same as a background response, $\beta_0$, as is required in the models described by Gennings 1997 and Gennings 1998.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 14-26.

With respect to the rejection of claim 1-13, independent claims 1 and 6 have hereby been amended to clarify what is meant by "relative ratios in a full and reduced set of chemicals" by incorporating the definition given in paragraph [0162] of the patent application. Namely, claims

1 and 6 now recite that the relative ratios in a full and a reduced set of chemicals are such that $\frac{a_{i(full)}}{a_{j(full)}} = \frac{a_{i(reduced)}}{a_{j(reduced)}}$ where $a_{i(full)}$ is the proportion of the $i^{th}$ chemical in the full mixture, $a_{j(full)}$ is the proportion of the $j^{th}$ chemical in the full mixture, $a_{i(reduced)}$ is the proportion of the $i^{th}$ chemical in the reduced (remaining) mixture, and $a_{j(reduced)}$ is the proportion of the $j^{th}$ chemical in the reduced mixture.

A subset or reduced ray which has the same relative ratios as a full ray is not described in either Gennings et al (1997) or in Gennings et al (1998). Multiple rays are described in Gennings et al (1998) such that "the first *c (<r)* rays are associated with each of the chemicals alone and that the remaining *r-c* rays are associated with the mixture rays." These are not required to have the same relative ratios as is the case for the present invention as claimed in claims 1 and 6. In addition, the example includes four rays where three are single chemical rays and one is the 70:1:29 mixture (see Table 4). According to the method taught by Gennings 1998 notation, $a_1$=70/100=0.70, $a_2$=1/100=0.01, and $a_3$=29/100=0.29 which sum to 1.0. Applicant submits that the case where a reduced subset has only one member cannot be used to illustrate the requirement for "same relative ratios" since it is not possible to form a "ratio" unless both $a_{i(reduced)}$ and $a_{j(reduced)}$ are not zero. If a subset contains only one agent, the ratio would then involve 0 in either the numerator or the denominator, both of which would result in a false statement that $\frac{a_{i(full)}}{a_{j(full)}} = \frac{a_{i(reduced)}}{a_{j(reduced)}}$. Gennings 1998 neither alludes to, shows or describes this requirement.

Gennings 1997 does not cure this defect. Gennings 1997 also does not teach full and reduced subset rays where $\frac{a_{i(full)}}{a_{j(full)}} = \frac{a_{i(reduced)}}{a_{j(reduced)}}$. Examiner refers to the hypothetical data illustrated in Figure 1 of Gennings 1997 as illustrating a subset with more than one member, stating that the hypothetical data is interpreted to be actual data wherein the plot can be "reconstructed using the data and relations in Gennings" 1997. This is incorrect.

Figure 1 illustrates a theoretical relationship of more than three dimensions (i.e. five dimensions: four chemicals plus a response) by holding all but three dimensions fixed. In particular, no rays of any type are specified in either Figure 1a or Figure 1b. Rather, the

hypothetical data is presented as a grid. The amount of chemicals 3 and 4 is 0 in Figure 1a and is fixed at 0.1 (see Figure legend) in Figure 1b, while the remaining three variables (chemical 1, chemical 2 and the response) are varied over the entire grid. Grids and rays are not mathematically equivalent. No "fixed- ratio ray design" as is required in claims 1-13 is employed or alluded to in Gennings 1997, and there is no requirement that relative ratios of amounts of agents in a subset with fewer members stay the same as in a fixed-ratio ray design such that $\frac{a_{i(full)}}{a_{j(full)}} = \frac{a_{i(reduced)}}{a_{j(reduced)}}$. Whether or not chemicals 3 and 4 are present, the amounts of chemicals change over a grid instead of along a fixed ratio ray where the ratio is constant (i.e. fixed). In contrast, the analysis described in claims 1 and 6 assumes and requires that the amounts of all chemicals in the analysis be present in fixed ratios according to a fixed ratio ray design.

In summary, there is no teaching of full and reduced (subset) fixed ratio rays in either Gennings 1997 or Gennings 1998, and no combination of Gennings 1997 and Gennings 1998 renders the subject matter of claims 1-13of the present application obvious.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-13.

**Claim Rejections: 35 USC § 103(a)**

Claims 30-31 stand rejected under 35 USC § 103(a) as unpatentable over Gennings 1997 and Gennings 1998 in view of Rosenberg (US 2003.0023951). This rejection is traversed.

Claims 30 and 31 have hereby been amended in a manner analogous to the amendment of claims 1 and 6, claims 30 and 31 corresponding to claims 1 and 6 by reciting software to carry out the methods recited therein. Applicant submits that, following the reasoning presented above for the patentability of amended claims 1 and 6, this amendment also renders the subject matter of claims 30 and 31 patentable, since neither Gennings 1997 or Gennings 1998 show, suggest or teach the use of subset rays, $\frac{a_{i(full)}}{a_{j(full)}} = \frac{a_{i(reduced)}}{a_{j(reduced)}}$. Rosenberg teaches on computer software to automate mathematical calculations and thus does not overcome the deficiencies of the two Gennings references. Therefore, no combination of Gennings 1997, Gennings 1998 and Rosenberg render the subject matter of claims 30 and 31 obvious.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

**Other matters**

Claim 14 is hereby amended to delete the phrase "from fixed ratio ray data". This feature is not necessary to distinguish the invention as claimed in claim 14 from the cited references, and properly appears instead in dependent claim 15.

Claims 17, 21, 25, 30 and 31 have hereby been amended to accord with the amendment to claims 1 and 6, as described above. Support for these amendments is found in the specification as described for claims 1 and 6.

**Concluding Remarks**

In view of the foregoing, it is requested that the application be reconsidered, that claims 1-26 and 30-31 be allowed, and that the application be passed to issue.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at 703-787-9400 (fax: 703-787-7557; email: ruth@wcc-ip.com) to discuss any other changes deemed necessary in a telephonic or personal interview.

If an extension of time is required for this response to be considered as being timely filed, a conditional petition is hereby made for such extension of time. Please charge any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,

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Appendix A

$$g(\mu)=\begin{cases}\beta_0+\sum_{r=1}^{c}\beta_r x_r, & x_c \le Q(x_1,x_2,\ldots,x_{c-1}) \Leftarrow \#1\\ \beta_0+\sum_{r=1}^{c}\beta_r x_r+\sum_{r=1}^{c-1}\sum_{s=r+1}^{c}\beta_{rs}x_r x_s+\sum_{r=1}^{c-2}\sum_{s=r+1}^{c-1}\sum_{u=s+1}^{c}\beta_{rsu}x_r x_s x_u+\ldots+\beta_{12\ldots c}x_1x_2\ldots x_c, & x_c > Q(x_1,x_2,\ldots,x_{c-1}) \Leftarrow \#2\end{cases}$$